Journal of
Cancer Science & Therapy

El-Sayed and Abdel-Wanis, J Cancer Sci Ther 2012, 4.6
DOI: 10.4172/1948-5956.1000132

Research Article Open Access

Comparison of Hypofractionated and Conventional Radiotherapy Protocols in Breast Cancer Patients: A Retrospective Study

Mohamed I. El-Sayed* **and Mostafa E. Abdel-Wanis**

Department of Radiation oncology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt

Abstract

Objectives: Conventional fractionated irradiation (CF) has major implications on both patient quality of life and radiotherapy (RT) departments. Hypofractionated (HF) RT schedule would be more convenient for patients and for health care providers. We retrospectively evaluated OAS, DFS, locoregional control, and treatment related toxicities, in patients treated with CF and HF schedules.

Methods: This retrospective study analyzed the medical records of female breast cancer patients with infiltrating duct carcinoma, and underwent surgery and received adjuvant systemic and radiation therapies.The schedule of adjuvant radiotherapy was divided into two groups; CF (n = 162), and HF (n = 181).The log-rank test examined differences in OAS and DFS rates. Data of radiation toxicities, and disease relapse in both CF and HF groups were compared using Chi-square test.

Results: The median follow up was 42 months (range: 6 - 127 months). Four-year OAS & DFS rates for the whole group were 86.5% & 83.8% respectively. There were no significant differences in 4-year OAS regarding age at diagnosis (p = 0.18, HR 0.66, 95% CI: 0.36 – 1.22), disease stage (p = 0.06), HR status (p = 0.1, HR 0.52, 95% CI: 0.241 – 1.135), type of surgery (p = 0.28, HR 1.44, 95% CI: 0.74 –2.79), and fractionation schedule (p = 0.12, HR 0.63, 95% CI: 0.35 – 1.34). Disease stage (p = 0.032, in favour of early stages) and fractionation schedule (p = 0.039, HR 0.553, 95% CI: 0.315 – 0.970 in favour of HF) were associated with significant differences in 4-year DFS rates.

Conclusion: Hypofractionated radiation therapy was safe and resulted in comparable OAS and disease relapse rates, to that in CF.

Keywords: Breast cancer; Fractionation; Survival

Introduction

Healthy breast tissue is sensitive to radiation fraction size, such that small changes in fraction size can lead to larger changes in radiation effects on these tissues [1]. Conventional breast and/or chest wall irradiation uses 2 Gys daily fractions, for 5-6 weeks. Such a long treatment schedule has major implications on both patient quality of life and RT departments [2,3].

Some investigators have hypothesized that breast cancer is as sensitive as normal breast tissue to fraction size. According to the hypothesis, small fraction sizes of 2.0 Gy or less offer no therapeutic advantage, and a more effective strategy would be to deliver fewer, larger fractions that result in a lower total radiation dose [1]. This short (hypofractionated) RT schedule would be more convenient for patients (especially those coming from remote areas to RT facilities) and for health care providers, as it would increase the turnover in RT departments. The use of a 16-fractions, instead of a 25-fractions regime, would save 900 treatment sessions per 100 patients (2500 - 1600 = 900). This corresponds to an additional 56 (900:16) patients who could be treated with the same number of fractions. This would result in substantial economic benefit as breast cancer patients represent the majority of patients treated in RT departments [4]. Although, the hypofractionated schedule had been studied in the western countries, there is no enough data about hypofractionation in Egyptian patients. Therefore, in order to confirm the feasibility of the hypofractionated RT for Egyptian breast cancer patients, we retrospectively evaluated OAS, DFS, locoregional control, and treatment related toxicities, of patients treated with the hypofractionated compared to that with the conventional RT.

Materials and Methods

The authors retrospectively analyzed the medical records of 343 breast cancer patients who were treated at Radiation therapy department, South Egypt Cancer Institute, Egypt, during the period from July, 2001 to January 2012. Patients included in the present study were required to have histologically proven invasive ductal carcinoma, and received adjuvant systemic and radiation therapies. This study was approved by the institutional review board and ethical committee. Eligible criteria included female breast cancer patients with histologically confirmed infiltrating duct carcinoma with no distant metastases. All patients underwent surgical resection (either MRM or BCS), and received adjuvant systemic and radiation therapies (either conventional or hypofractionated radiation).

Radiation techniques and schedules

Patients who underwent BCS were simulated with 3D planning, whereas those who underwent MRM were simulated with 2D technique.

***Corresponding author:** Mohamed I. El-sayed, MD, Department of Radiation oncology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt, Zip code: 71111, Tel: (0020) 1222953887; Fax: (0020) 882348609; E-mail: mohebel@yahoo.co.uk

Received May 03, 2011; **Accepted** June 04, 2012; **Published** June 06, 2012

Citation: El-Sayed MI, Abdel-Wanis ME (2012) Comparison of Hypofractionated and Conventional Radiotherapy Protocols in Breast Cancer Patients: A Retrospective Study. J Cancer Sci Ther 4: 158-163. doi:10.4172/1948-5956.1000132

Target volumes included breast and chest wall in patients with BCS or chest wall in mastectomized patients [and ipsilateral supraclavicular region in cases of positive axillary lymph nodes]. Medial and lateral tangential fields to treat breast and/or chest wall and anteroposterior ipsilateral supraclavicular field were used with 6 MV photon beams. The foot of the treatment couch was turned (by degrees depending on the length of the tangential fields) away from the collimator so that the two cephalad tangential field margins crossed the patient's chest in a straight line that was parallel with the caudal supraclavicular field margins to avoid overlap of the two fields. The treatment plan was acceptable if ≤ 10% of the heart volume and ≤ 25% of the ipsilateral lung volume received 25 Gy (in case of 3D planning), [5] or maximum central lung distance ≤ 3 cm (in case of 2D planning).

The schedule of adjuvant radiotherapy was divided into two groups during that period. One hundred and Sixty two patients received 2.0 Gy daily fractions for 25 fractions to a total dose of 50 Gy, designated as conventional group. One hundred and eighty one patients received 2.65 Gy daily fractions for 16 fractions to a total dose of 42.5 Gy (n = 131) or 3 Gy daily fractions for 13 fractions to a total dose of 39 Gy (n = 50), designated as hypofractionated group. A boost dose of 14 Gy in 7 fractions to tumor site using 12 Mev electrons was given to patients ≤ 50 years of age, who underwent conservative surgery.

Assessment of treatment outcomes and toxicities

The primary endpoints were overall survival, disease free survival, and disease relapse, in both groups. Secondary endpoint was radiation toxicities. Disease free survival (DFS) was defined as the interval from enrollment of patients to the date of first event (relapse, progression, or death from any cause) or to the date of last follow-up. Overall survival (OAS) was defined as the interval from enrollment to the date of death from any cause or to last follow-up. Early and late toxicity were scored according to the Radiation Therapy Oncology Group criteria in both groups of patients [6].

Statistical analysis

The study cutoff point was February, 2012. Disease free survival and OAS rates were estimated using Graphed prism program, and compared between the conventional and hypofractionated groups by the log-rank test. Data of radiation related skin toxicities, and pneumonitis and disease relapse in the two studied groups were compared using Chi-square test. The p-value reports are two-tailed and an alpha level of 0.05 was used to assess statistical significance.

Results

The 343 cases included in the present study showed an age incidence which ranged from 30-69 years, with the median age of 47 years. The majority of patients were of < 50 years of age (202 patients, 59%), had stage II & III disease (316 patients, 92%), had HR positive disease (269 patients, 78%), and underwent MRM (243 patients, 71%). There were even distribution of patients in both hypofractionation and conventional radiation groups, regarding patients' age at diagnosis. However, there were significant difference regarding disease stage (p < 0.0001), HR status (p = 0.018), and type of surgery (p < 0.0001) (Table 1).

After a median follow up of 42 months, 4-year OAS & DFS rates for the whole group were 86.5% & 83.8% respectively. There were no significant differences in 4-year OAS regarding any of the studied factors; namely age at diagnosis (p = 0.18, HR 0.66, 95% CI 0.36 – 1.22), disease stage (p = 0.06), HR status (p = 0.1, HR 0.52, 95% CI: 0.241 – 1.135), type of surgery (p = 0.28, HR 1.44, 95% CI 0.74 – 2.79), and fractionation schedule (p = 0.12, HR 0.63, 95% CI: 0.35 – 1.34). Disease stage (100% for stage I, 80% for stage II, 78% for stage III, p = 0.032) and fractionation schedule (85.6% for HF, 81% for CF, p = 0.039, HR 0.553, 95% CI: 0.315 – 0.970) were associated with significant differences in 4-year DFS rates (Table 2, Figures 1 & 2).

In the present study, univariate analysis showed that patients given hypofractionated radiotherapy had similar 4-year OAS rates regarding patient's age (p = 0.176), hormonal receptor status (p = 0.22), and type of surgery (p = 0.27). Although there were no differences of 4-year OAS rates between patients according to disease stage (p = 0.06) (Table 2), stratification analysis by fractionation schedule used, revealed that these patients showed statistically significant OAS advantage in patients with early disease stages (I & II) as compared to those with stage III disease (p = 0.029) (Table 3).

In the current study, the incidences of grade 1 dermatitis were 48% and 52.5% in patients with hypofractionated and conventional radiation therapy, respectively, and grade 2 dermatitis, were 9% and 25%, respectively (p < 0.0001). Patients with grade 2 dermatitis showed < 1 week of treatment interruption. Incidences of late skin toxicity (10% versus 5%, p = 0.144), and grade 2 radiation induced pneumonitis (3% versus 5.5%, p = 0.22) were comparable between hypofractionated

Variable	HF (n = 181)		CF (n = 162)		Total (N = 343)		p value
	No	%	No	%	No	%	
Age at diagnosis:							
* <50 years	103	56.9	99	61.1	202	58.9	p = 0.43
* ≥50 years	78	43.1	63	38.9	141	41.1	
Disease stage:							
* Stage I	13	7.2	14	8.6	27	7.9	
* Stage II	112	61.9	62	38.3	174	50.7	p < 0.0001
* Stage III	56	30.9	86	53.1	142	41.4	
HR Status:							
* HR +ve	133	73.5	136	83.9	269	78.4	p = 0.018
* HR –ve	48	26.5	26	16.1	74	21.6	
Type of surgery:							
* BCS	22	12.2	78	48.1	100	29.2	p < 0.0001
* MRM	159	87.8	84	51.9	243	70.8	

Table 1: Patients' characteristics in hypofractionated and conventional radiotherapy groups.

and conventional radiation groups, respectively. Regarding disease relapse, the incidence was comparable between hypofractionated and conventional radiation groups (9% versus 12%, respectively, p = 0.38) (Table 4).

Discussion

Data from randomized trials regarding hypofractionation for treatment of women with breast cancer, confirm the safety and efficacy of schedules using fraction sizes of around 3 Gy, provided the correct downward adjustments to total dose are made [7].

Hypofractionated radiation therapy offers the advantage of a more efficient and productive use of radiotherapy departments resources; whether machine time, staffing of treatment units, lower expenses in addition to far better patients convenience [8]. On the other hand, hypofractionation, with larger radiation dose per fraction increases the possibility of late normal tissue damage [9,10]. However, the linear-quadratic model predicts that the normal tissue toxicity is not increased when the fraction dose is modestly increased and the total dose is reduced [7]. This is confirmed by results of many trials where hypofractionated radiotherapy protocols are as effective as the conventional radiation of 50 Gy in 25 fractions [11,12], regardless of disease stage or type of breast surgery [13].

Although the safety and efficacy of hyperfractionation have been confirmed by a number of clinical trials in western countries, there remains much controversy especially at the level of the understanding of the underlying radiobiological mechanisms. The tool most commonly used for quantitative predictions of dose / fractionation dependencies in radiotherapy is the mechanistically-based linear-quadratic (LQ) model [14-16]. The LQ formalism is now almost universally used for calculating radiotherapeutic isoeffect doses for different fractionation/protraction schemes. Brenner [17], stated that, to date, there is no evidence of problems when LQ has been applied in the clinic. In contrast, Kirkpatrick et al. [18] stated that the underlying mechanisms implied by the LQ model do not reflect the vascular and stromal damage produced at the high doses per fraction encountered in radiosurgery and ignore the impact of radioresistant subpopulations of cells. The appropriate modeling of both tumor control and normal tissue toxicity in radiosurgery requires the application of emerging understanding of molecular-, cellular-, and tissue-level effects of high-dose/fraction-ionizing radiation and the role of cancer stem cells.

Variable	4-year OAS rate (%)	4-year DFS rate (%)
Age at diagnosis:		
<50 years	88.4	86.2
≥50 years	83.2	79.4
P value	p = 0.18, HR 0.66, 95% CI 0.36 – 1.22	p = 0.21, HR 0.69 95% CI 0.39 – 1.23
Disease stage:		
Stage I	100	100
Stage II	88.8	79.7
Stage III	79.7	77.8
P value	p = 0.06	p = 0.032
HR Status:		
HR Positive	87.5	85.1
HR Negative	82.7	78.2
P value	p = 0.1, HR 0.52, 95% CI: 0.241 – 1.135	p = 0.07, HR 0.52, 95% CI: 0.251 – 1.06
Type of surgery:		
BCS	87.5	82.6
MRM	86	84.2
P value	p = 0.28, HR 1.44, 95% CI: 0.74 – 2.79	p = 0.96, HR 1.01, 95% CI: 0.547 – 1.88
Radiation dose & fractionation:		
HF	90.4	85.6
CF	82.5	80.9
P value	p = 0.12, HR 0.63, 95% CI: 0.35 – 1.34	p = 0.039, HR 0.553, 95% CI: 0.315 – 0.970

Table 2: Four year OAS and DFS rates in 343 breast cancer patients according to prognostic factors: [4-year OAS & DFS rates for the whole group were 86.5% and 83.8% respectively].

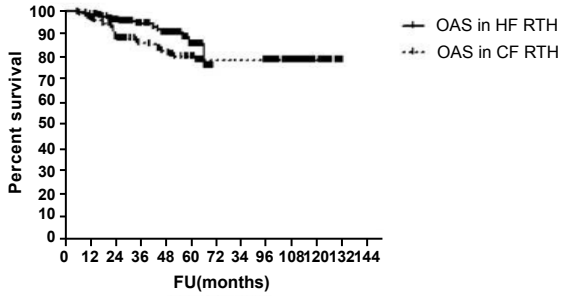

Figure 1: OAS of breast cancer patients according to fractionation.

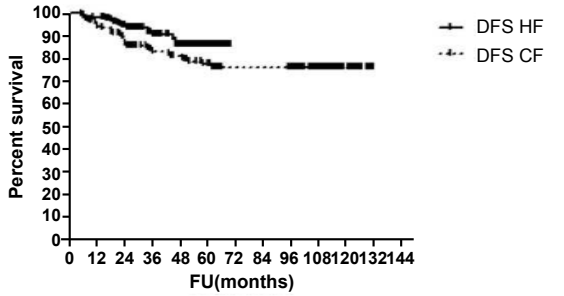

Figure 2: DFS of breast cancer patients according to fractionation.

Cancer stem cells (CSCs) are a sub-population of self-renewing and expanding stem cells. CSCs were isolated from solid tumors, including, breast cancer [19]. A large body of evidence points to the fact that CSCs are particularly resistant to radiotherapy and chemotherapy [20]. Phillips et al. [21], and Bao et al. [22], suggested that radioresistance may be a general property of CSCs and that this may be due to their ability to more efficiently repair DNA than non-CSCs. In light of these studies, it is clearer that identifying and characterizing CSCs is of great importance and will lead to new therapeutic avenues. The effects of radiation on CSCs rather than the bulk of a tumor could prove to be more sensitive predictors of treatment outcome than traditional measures of treatment response [23].

The current study being retrospective in nature, suffers a major deficiency as the two groups (hypofractionation and conventional fractionation groups) had different tumor/clinical characteristics to begin with which might cause bias. However, it confirms the feasibility of hypofractionated radiotherapy in breast cancer patients. Most of breast cancer patients in the present study were ≥ 50 years of age, had stage II and III disease, and underwent MRM. Regarding patient and

Variable	OAS		DFS	
Age at diagnosis:	HF	CF	HF	CF
* <50 years	95.2%	81.8%	89.9%	80.8%
* ≥50 years	84.7%	81.9%	80.3%	79%
P value	p = 0.176, HR:0.504, 95% CI: 0.187-1.360	p = 0.55, HR:0.79, 95% CI: 0.36-1.73	p = 0.192, HR:0.527, 95% CI: 0.201-1.38	p = 0.47, HR:0.76, 95% CI: 0.364-1.590
Disease stage:				
* Stage I	100%	100%	100%	100%
* Stage II	92.3%	80.5%	86.2%	78.9%
* Stage III	88.5%	78.4%	88.5%	76.3%
P value				
HR Status:				
* HR Positive	91.7%	83.7 %	86.9 %	81.7%
* HR Negative	86%	70.4%	79.6 %	65.5%
P value	p = 0.22, HR: 0.46, 95% CI: 0.131-1.610	p = 0.157, HR: 0.476, 95% CI: 0.170-1.33	p = 0.43, HR: 0.62, 95% CI: 0.195-1.990	p = 0.045,HR: 0.373, 95% CI: 0.143-0.978
Type of surgery:				
* BCS	89.8%	85.9%	89.8%	80.2%
* MRM	91%	79.4%	86 %	79.4%
P value	p = 0.266, HR:3.33, 95% CI: 0.401-27.66	p = 0.091, HR:1.88, 95% CI: 0.90-3.93	p = 0.577, HR:1.65, 95% CI: 0.281-9.73	p = 0.597, HR:1.204, 95% CI: 0.605-2.397

Table 3: Four year OAS and DFS rates in HF and CF groups of patients according to prognostic factors.

Variable	HF		CF		Total		p value
	No	%	No	%	No	%	
Acute skin toxicity							
No dermatitis (G0)	78	43.1	36	22.2	114	33.2	<0.0001
Grade 1 dermatitis (G1)	87	48.1	85	55.5	172	50.2	
Grade 2 dermatitis (G2)	16	8.8	41	25.3	57	16.6	
Late skin toxicity							
G0	93/103	90.3	120/126	95.2	213/229	93	0.144
G1	10/103	9.7	6/126	4.8	16/229	7	
Radiation pneumonitis							
G0	159	87.8	132	81.5	291	84.8	
G1	17	9.4	21	13	38	11.1	0.22
G2	5	2.8	9	5.5	14	4.1	
Disease relapse							
yes	17	9.4	20	12.3	37	10.8	0.38
no	164	90.6	142	87.7	306	89.2	

Table 4: Radiation related toxicities and disease relapse in hypofractionated and conventional radiotherapy groups.

tumor characteristics, patients' age and hormonal receptor status did not differ significantly between conventional and hypofractionation groups (p = 0.43 and p = 0.06 respectively). On the other hand, significant difference regarding incidence of disease stage (p < 0.0001) occurred between the two groups. In literature, reported studies showed that the two groups showed significantly different disease stage distribution. These studies, however, showed even distribution of patients' age and hormonal receptor status [11,13,24] between the two groups. In the present study, 29% (100 patients) underwent BCS. This is comparable to what was reported by Schwartz et al. [25], where BCS was done in 36% of patients.

With a median follow up of 42 months (range 6-132 months), the 4 year OAS and DFS rates were 86.5% and 83.8% respectively. In univariate analysis, there were no statistically significant difference in 4-year OAS and DFS rates regarding patients' age (p = 0.18 and p = 0.21 respectively), hormonal receptor status (p = 0.1 and p = 0.07 respectively) and type of surgery (p = 0.28 and p = 0.96 respectively). This matched with reported studies, where patients' age < 50 and ≥ 50 years [26], estrogen receptor status [26] and type of surgery (BCS, and MRM) [2] had no significant effect on survival. Although there were no differences of 4-year OAS rates between patients according to various clinical variables, stratification analysis by fractionation schedule used, showed that patients given hypofractionated radiotherapy had statistically significant OAS advantage in patients with early disease stages (I & II) as compared to those with stage III disease (p = 0.029). However, the present study, showed only significant higher 4- year DFS rates (p = 0.032) in patients with stage I disease than those in patients with more advanced disease. This is matched with Turkish study, where disease stage was significant prognostic factor for DFS [27].

Patients in the hypofractionated radiotherapy group in the

current study, showed comparable 4-year OAS rate with those in the conventional schedule (90.4% versus 82.5%, p = 0.12, HR 0.63, 95% CI: 0.35 – 1.34). In literature, four studies [28-32], reported overall survival (Canadian, START A, START B and Spooner). These studies confirmed our results, and reported that there was no evidence that hypofractionated radiotherapy was associated with a statistically significantly difference in overall survival. In a randomized Canadian trial, Whelan et al. [28] reported equivalent results (regarding local control, survival, and post-radiation effects) between the standard fractionation schedule of 50 Gy in 25 fractions and a hypofractionated scheme of 42.5 Gy in 16 fractions over 22 days. This study has been updated recently and, results have not changed after a 10-year follow-up [29], where the probability of survival over time was similar in the hypofractionated-radiation and conventional radiation groups (p = 0.79). At 10 years, the probability of survival was 84.4% in the conventional radiation group as compared with 84.6% in the hypofractionated-radiation group (absolute difference, −0.2 percentage points; 95% CI, − 4.3 to 4.0). The START A trial [30], START B trial [31], and Spooner [32], reported also that, there was no evidence that any hypofractionated radiotherapy regimen was associated with a worse overall survival rate.

In the present study, univariate analysis showed that patients given hypofractionated radiotherapy had similar OAS rates regarding patient's age (p = 0.176), hormonal receptor status (p = 0.22), and type of surgery (p = 0.27). On the other hand, patients with early disease stage (I & II) showed statistically significant higher OAS than those with stage III disease (p = 0.029). In a subgroup analysis of a randomized trial [29], showed that the effect of hypofractionated radiation was similar regardless of the patient's age, tumor size, estrogen-receptor status, or use or nonuse of systemic therapy.

In the current study, patients with hypofractionated radiation was safe and showed acceptable toxicity rate with only 9% incidence of grade II dermatitis and resulted in < 1 week treatment interruption. Moreover, it was statistically significant lower than in patients treated with conventional radiotherapy (9% versus 25%, p < 0.0001). Incidences of late skin toxicity (10% versus 5%, p = 0.144), and grade 2 radiation induced pneumonitis (3% versus 5.5%, p = 0.22) were comparable between hypofractionated and conventional radiation arms. This is consistent with the combined results from the START A and START B trials, where a change in skin appearance occurred significantly less often in the hypofractionated radiation arm (39 Gy and 40 Gy arms) when compared with the 50 Gy arm (39 Gy HR 0.63 95% CI 0.47, 0.84, p = 0.0019 and 40 Gy HR 0.76 95% CI 0.60, 0.97, p = 0.0262) [33]. However, most trials reported that there was no difference in adverse events and toxicity between hypofractionated and conventional RTH. The incidence of ischemic heart disease, symptomatic rib fracture and symptomatic lung fibrosis was low, with no differences between the study arms [31].

The current study showed that the incidence of disease relapse was comparable between hypofractionated and conventional radiation arms (9% versus 12%, p = 0.38). This is in agreement with results of START A [30] and START B trials [31]. The START A trial randomized 2236 patients from 17 centres across the UK and reported that 41.6 Gy/13 fractions or 39 Gy/13 fractions are similar to 50 Gy/25 fractions in terms of local-regional tumor control. The START A trial [30] showed that after a median follow-up of 5.1 years, the rate of local-regional tumor relapse at 5 years was 3.6% [95% confidence interval (CI): 2.2%-5.1%] after 50 Gy, 3.5% (95% CI: 2.1%-4.3%) after 41.6 Gy, and 5.2% (95% CI: 3.5%-6.9%) after 39 Gy. The estimated absolute differences in 5-year local-regional relapse rates compared with 50 Gy were 0.2% (95% CI: -1.3%-2.6%) after 41.6 Gy and 0.9% (95% CI: -0.8%-3.7%) after 39 Gy. The START B trial [31] randomized 2215 patients from 23 centers across the UK and reported that after a median follow-up of 6.0 years, the rate of local-regional tumor relapse at 5 years was 2.2% (95% CI: 1.3%-3.1%) in the 40 Gy group and 3.3% (95% CI: 2.2%-4.5%) in the 50 Gy group. Our result is matched also with what was reported by a retrospective study [13] where, it was found that, 5 year locoregional control rate was 86.6% in conventional group and 85.8% in hypofractionated group. The log-rank test showed no statistical difference (p = 0.852).

Conclusions and Recommendations

Recent randomized trials justify the routine use of HF for adjuvant radiotherapy in women with breast cancer. Hypofractionated radiation therapy resulted in OAS rate comparable to that of CF (50 Gy/25 fractions/5weeks) without evidence of inferior local tumor control or higher adverse effects. Hypofractionated radiation therapy can be recommended as safe and effective alternatives to CF for whole-breast or postmastectomy chest wall radiotherapy.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Mohamed I. El-Sayed participated in the patient diagnosis, management, statistical analysis, and manuscript writing. Mostafa E. Abdel-Wanis participated in the patient diagnosis, and management.

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